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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/957,456	09/21/2001	Tully Michael Underhill	9611-26	2501

7590 11/26/2003

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/957,456	UNDERHILL ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 07/22/03 has been acknowledged.

Claims 2-3, 11, 14-26 are canceled.

Claims 1, 4, 6 and 12 are amended.

Claims 1, 4-10 and 12-13 are pending and are examined in this office action.

Applicants are required to follow **Amendment Practice** under revised **37 CFR §1.121** (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Applicant's arguments with respect to claims 1, 4-10 and 12-13 have been considered but are moot in view of the new ground(s) of rejection as necessitated by recent amendment filed on 07/2203.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed (after the recent amendment) encompasses a method of identifying a modulator of chondrogenesis by transiently transfecting the primary limb mesenchymal cells with a nucleic acid construct comprising a reporter gene that comprises a sequence that binds to an endogenous protein in the cells that is changed upon chondroblast or chondrocyte differentiation in response to the addition of a test compound to the transfected cells, wherein a change in reporter gene activity indicates that the test compound modulates the chondroblast or chondrocyte differentiation.

The specification as filed discloses a reporter gene construct comprising an enhancer element (Sox9 binding sequence upstream of the mouse Col II minimal promoter, -89 to +13) that is responsive to the transcription factor Sox9 (spec. page 17, example-1). However, the specification as filed fails to disclose any other genetic construct that comprises any other nucleotide sequence that binds to any other endogenous protein in the cells, wherein a change in reporter gene activity operatively linked to the response element indicates that the test compound modulates the chondroblast or chondrocyte differentiation. In addition the specification as filed fails to disclose what comprises the claimed pGL3(4X48) nucleic acid construct, since the it fails to disclose what are the structural and/or functional limitations of pGl3(4X48). Furthermore, the specification even fails to identify any 48-bp fragment (Sox9 response element) that is responsive to transcription factor Sox9.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see

http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only discloses a reporter gene construct comprising an enhancer element (Sox9 binding sequence upstream of the mouse Col II minimal promoter, -89 to +13) that is responsive to the transcription factor Sox9. The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the response element comprising a

nucleic acid sequences that (as claimed) has been defined only by a statement of function that broadly encompasses modulation by any endogenous cellular protein, which conveyed no distinguishing information about the identity of the claimed response element and the transcription factor, such as its relevant structural or physical characteristics.

In addition, the instant specification would fails to meet written description requirement for the deposited biological material. see Deposit of Biological Materials for Patent Purposes, Final Rule, 54 FR 34,864 (August 22, 1989) ("The requirement for a specific identification is consistent with the description requirement of the first paragraph of 35 U.S.C. 112, and to provide an antecedent basis for the biological material which either has been or will be deposited before the patent is granted." Id. at 34,876. "*The description must be sufficient to permit verification that the deposited biological material is in fact that disclosed. Once the patent issues, the description must be sufficient to aid in the resolution of questions of infringement.*" Id. At 34,880.). Such a deposit is not a substitute for a written description of the claimed invention. The written description of the deposited material needs to be as complete as possible because the examination for patentability proceeds solely on the basis of the written description. See, e.g., In re Lundak, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985). See also 54 FR at 34,880 ("As a general rule, the more information that is provided about a particular deposited biological material, the better the examiner will be able to compare the identity and characteristics of the deposited biological material with the prior art."). In instant case applicant's referral to the pGL3(4X48) on page 17 of the specification is insufficient

assurance that all written description requirements for the deposited biological material had been met. It is unclear what would be the nucleotide sequence of pGL3(4X48) if a biological deposit had been made. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus *(which encompasses any response element and its corresponding transcriptional factor that regulates chondrogenesis)* because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1, 4, 9-10 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of identifying a modulator of chondrogenesis by transiently transfecting the primary limb mesenchymal cells with a nucleic acid construct comprising Sox9 response element (*Col2a1*) operatively linked to a reporter gene, wherein a change in reporter gene activity indicates that the test compound modulates the chondroblast or chondrocyte differentiation, does not reasonably provide enablement for the method (as claimed) that requires the use of any response element which binds to any endogenous protein in mesenchymal cells in the process of chondrogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of Invention: Invention relates to a method of identifying a modulator of primary limb mesenchymal differentiation.

Breadth of Claims and Guidance Provided in the Specification: The scope of invention as claimed (after the recent amendment) encompasses a method of identifying a modulator of chondrogenesis by transiently transfecting the primary limb mesenchymal cells with a nucleic acid construct comprising a reporter gene that comprises a sequence that binds to an endogenous protein in the cells that is changed upon chondroblast or chondrocyte differentiation in response to the addition of a test compound to the transfected cells, wherein a change in reporter gene activity indicates that the test compound modulates the chondroblast or chondrocyte differentiation.

The specification as filed discloses a reporter gene construct comprising an enhancer element (Sox9 binding sequence upstream of the mouse Col II minimal promoter, -89 to +13) that is responsive to the transcription factor Sox9 (spec. page 17, example-1). However, the specification as filed fails to disclose any other genetic construct that comprises any other nucleotide sequence that binds to any other endogenous protein in the cells, wherein a change in reporter gene activity operatively linked to the response element indicates that the test compound modulates the chondroblast or chondrocyte differentiation. In addition the specification as filed fails to disclose what comprises the claimed pGL3(4X48) nucleic acid construct, since the it fails to disclose what are the structural and/or functional limitations of pGl3(4X48). Furthermore, the specification even fails to identify any 48-bp fragment (Sox9 response element) that is responsive to transcription factor Sox9. Therefore it is unclear how one skill in the art would exercise the invention as claimed without the disclosure of structural limitations of the claimed pGl3(4X48) construct.

State of Art and Predictability: Chondrogenesis is a multi step process culminating in the establishment of a precisely patterned template for bone formation. During chondrogenesis, numerous factors act together to coordinate commitment and differentiation of skeletal progenitors, and these processes occur in a spatial- and temporal-specific manner. The proper size and shape of the developing skeletal elements relies on the appropriate control of chondroblast differentiation. To date, the Sox genes, L-5, -6, and -9 are the only known transcription factors through which this control is achieved. These genes contain a high mobility group domain and belong to the Sox family of proteins that are homologous to the protein encoded by Sry (sex-determining region of Y chromosome). Of this group, Sox9 is known to play an essential role in establishing the pre cartilaginous condensations and in initiating chondroblast differentiation. Specifically, Sox9 binds to a region within the first intron of the type II collagen gene (Col2a1) to regulate its transcription. Sox9 activation of Col2a1 can be considered to be a hallmark event in cartilage formation (Weston et al, The Journal of Cell Biology, 158(1):39-51, 2002 see abstract pages 40 , col.1, pare 3). Similarly in the instant case specification only teaches a reporter gene construct comprising an enhancer element (Sox9 binding sequence upstream of the mouse col II minimal promoter, -89 to +13) that is responsive to the transcription factor Sox9 (spec. page 17, example-1). The specification as filed fails to disclose any other genetic construct that comprises any other nucleotide sequence that binds to any other endogenous protein in the cells that are changed upon chondroblast or chondrocyte differentiation.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The courts have clearly stated that: a specification need not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

In addition screening compounds that modulates chondrogenesis by modulating any response element by any transcriptional factor is not considered routine in the art and without sufficient guidance to a specific genetic construct comprising a specific response element that binds to a specific transcription factor the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex

parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

In addition applicant argument that "a biological deposit is not required as one ordinary skill in the art could readily prepare the claimed plasmid without undue experimentation" has been found moot, since the elements required for practicing the invention as claimed are not readily available to the public or obtainable by repeatable method set forth in the instant specification. In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient (see MPEP 2402, 37CFR 1.802). In instant case applicant's referral to the pGL3(4X48) on page 17 of the specification is insufficient assurance that all written description and enablement requirements has been met (*supra*). The specification fails to disclose what comprises the nucleotide sequence of pGL3(4X48) which renders the genetic construct (as claimed) selectively responsive to the Sox9 transcriptional factor. Therefore the elements required for practicing the instant invention are not readily available to the public or obtainable by repeatable method set forth in the instant specification.

Claim Rejections - 35 USC § 103

Claims 1, 4-8 and 12-13 rejected under 35 U.S.C. 103(a) as being unpatentable over LeFebvre et al (Matrix Biology 16;529-540, 1998) or LeFebvre et al (EMBO J. 17(19);5718-5733, 1998) in view of Healy et al (Dev. Dyn. 215:68-78, 1999, *ref of record)*, for the same reasons of record as set forth in the office action mailed on 04/22/03.

Response to arguments: Applicant argues that, the claims have been amended in order to specify that the cells used in the assay are primary limb mesenchymal cells and the reporter gene contains a sequence that binds to an endogenous protein in the cells. None of the art cited by the office discloses or suggests an assay for identifying modulator of chondrogenesis containing these elements. Applicant further argues that primary limb mesencchymal cells provides amore accurate in vitro model system to study chondrogenesis.

However, this is found NOT persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art

clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In instant case LeFebvre (Matrix Biol.) clearly teaches that Sox9 is a typical transcriptional factor that regulates chondrocyte differentiation in mesenchymal cell (see claims 4-8). Regarding claims 1 and 12-13, the cited art further teaches that Collagen type II (col2a1) is a chondrocyte specific enhancer, which is a direct target for Sox9 (abstract, page 538 fig-5). The cited art further teaches making of Col2a1-reporter gene constructs containing chondrocyte specific enhancer sequences operatively linked to a luciferase gene, which is strongly activated upon cotransfection of Sox9 expression plasmid (page 534, col.2). The cited art further teaches a method of identifying a modulator of chondrogenesis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblasts or chondrocytes (page 534, fig-4). Given the broadest reasonable interpretation the transfection of Sox9 plasmid clearly anticipate the nucleic acid molecule encoding a test compound that modulates the process of chondrogenesis (see claim 13). In addition the cited art teaches that both the sox9 and Col2a1 expression levels peak when very active chondrogenesis is in progress (page 533 col.1 para.2). Similarly LeFebvre (EMBO J.) teaches a method of identifying a modulator of chondrogeneis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblast or chondrocyte with a

genetic construct (p309 Co2a1-βgeo) encoding a 48 bp Cola1 enhancer element operatively linked to a β-gal reporter gene (page 5732, col.1 para 4). The cited art teaches that transient transfection of primary chondrocytes obtained from ribs of newborn mice (page 5729, fig-7, page 532 col.1 para.3). Even though the LeFebvre teaches the transfection of cells of mesenchymal origin the cited art does not teach the transfection of primary limb mesenchymal cells.

Healy teaches regulation and role of Sox9 in cartilage formation (page 69 abstract). The cited art teaches transfection of a retroviral vector encoding Sox9 gene into the primary limb mesenchymal cells in chicken embryonic cells (page 77 col.1). The cited art further teaches preparation of limb bud mesenchymal culaturre that leads to precartilageous condensations (page 77, col.1, page 75, col.2). The cited art further teaches transfection of isolated limb mesenchymal cells with a retroviral vector encoding alkaline-phosphatase reporter gene (page 73, fig-4).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of LeFebrve by substituting the mesenchymal cells with primary limb mesenchymal cells as taught by Healy. One would have been motivated to do so because primary limb mesenchymal cells allow direct assessment of the effects of Sox9 expression in skeletonogenic and chondrogenic tissues. One would have a reasonable expectation of success because tranfection of primary limb mesenchymal is well with in the reach of one ordinary skill in the art (see Healy). Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER